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SPECIFICITY OF BIOLOGICAL METABOLISM

[Following is the translation of an article
by V. A. Engel'gardt entitled "Spetsifichnost
biologicheskogo obmena veshchestv" (English
version above) in "Voprosy filosofii" (Prob-
lems in philosophy), No.7, 1960, Moscow,
pages 113-123.]

Chemistry plays a leading role in the study
of the specific features of metabolism. In order to clarify
the specificity of metabolism, let us first examine the
attributes of life.

These attributes are extremely varied.
They include the specifics of the chemical composition of
living matter, the specifics of nature and of the most impor-
tant properties of chemical materials, that enter into the
structure of living organisms, including primarily the most
important biological polymers — albumens, nucleinic acids
and polysaccharides.

Together with this unique chemical compo-

sition , that may be characterized as chemical statics,
is the unique nature of the chemical c o n v e r s i o n s,
that in their totality constitute what we call metabolism.
The inalienable property of all living matter is its ability
of autoreproduction, to reproduce its likeness. The proper-
ty of excitation or stimulation may be observed in different
degrees of perfection and complexity throughout the entire
period of existence of a living world. It is precisely on
that property that the entire complexity of the relationships
between an organism and the medium rests. The ability to
move is, as a rule, to a greater or lesser extent an
attrbute of living matter.

The nature of any living object, be it the most
primitive, is so perfect, and the principle of wholeness
that ties together the listed attributes in an indivisible
                                  any attempt
unity, is so fully expressed, that/to establish some kind
of hierarchy among these attributes and determine their
interdependence, to decide what is more important, or primary,
and what is secondary, subordinate or duplicated is very
difficult and, in principle even disputable.

But clearly admitting the difficulty and
questionable nature of the establishment of such an hierar-
chy, we nevertheless have reason to believe, that to a
certain degree this can be done.

It seems to us that two of the attributes listed above are basic and primary: the specificity of the composition of living things and the unique nature of chemical conversions, the specificity of metabolism.

What is it that gives us a basis for believeing that these are the most important attributes, that they are primary? This may be done on the basis that all other properties of living matter, no matter how important and inalienable they may be, derive to some extent from the two primary properties mentioned above.

The following proposition is perfectly obvious and probably does not need to be argued: any properties of living organisms in the final analysis are a function of that materialistic substrate of which the living substance is made. The scientific forecast of Engels is amazing in that it permitted him almost one hundred years ago, during a period of infancy in our knowledge of the chemistry of living things, to characterize albumens with unusual perspicacity as being the prime base of all living matter. The question of the specifics of the materialistic substrate of living organisms is so clear and indisputable, that it may be taken as an axiom or a postulate.

Concerning the place of metabolism in the hierarchy of the attributes of living matter, a few words must be

said. In Engels' definition, that has just been given, as decisive a position is given to metabolism as to albumens. In the days of Engels, knowledge of the character of metabolism processes was extremely poor, and science still knew nothing definite about the degree to which the metabolism process is linked to the manifestation of organic functions, of the extent to which metabolic reactions are linked to the manifestations of living activity, to these or other organic functions, and of the degree to which metabolism's reactions are a primary and motive force of the properties that characterize living beings. It is natural, therefore, that Engels limited himself in his characterization of the biological role of metabolism by to its significance in sustaining the normal unstable material base of living organisms, i.e. of the albumen in their protoplasm. He stressed the need of continuous metabolism for the preservation of biologically important properties.

The decades that have passed since that time have brought a great enrichment and a broadening of our concepts of the metabolism processes themselves, and of their role as a source of/the motive force, the primary base of all of life's functions without exception, of all manifestations of living activity.

Growth, reproduction, moveability, excitabi-

lity, the property of being able to react to outside changes, all these are properties of living matter, and, in the final analysis, are linked to definite chemical conversions, lacking which not a single one of these manifestations of life could be accomplished. It is perfectly clear that the connection between metabolism and the manifestation of life is often exercised through the medium of the participating micro- and macrostructure of the physical organization of the living object, the participation of electric phenomena, etc. But the basis, the foundation is always the same: the primary factors are strict and well defined metabolism processes, that proceed in an orderly fashion, and are usually coordinated in a multitude of extremely complex stages.

From this it follows necessarily that a knowledge of the nature and substance of these secondary attributes of life mentioned above is impossible, without a detailed study of the biochemical reactions, i.e. the processes of metabolism.

This is what prompted us to place these processes in the forefront of the hierarchy of life's attributes.

It should be said that, if we can now draw such a conclusion based on concrete facts, then great minds in the realm of natural sciences, our scientific leaders

have understood and have formulated the role of chemistry,
in an understanding of the living world centuries or a half
a century before factual, experimental material was available
that today daily and hourly confirms these thoughts of ours.

Almost 200 years ago, in 1785, the great
Lavoisier, the creator of quantitative chemistry, found that
in burning matter in a laboratory and in its processing
in the course of the breathing process, the organism absorbs
the same amount of oxygen, as much energy is generated in
the form of heat and the same amounts of the same final
products are created. And he formulated his conclusion in
a monumental form: "Life is a chemical function".

The chemist Pasteur destroyed the myth of
spontaneous conception. This is his greatest service to
natural science. As a matter of curiosity, he simultaneously
pushed unstable investigators into the bog of another idea-
listic concept — that of the necessity to acknowledge the
initial creative act. To refute this distortion it became
necessary to disseminate the correct materialistic understan-
ding of the world. In the special chemical work of Pasteur
we find a solution to a series of fundamental problems that
confronted biological science in those days.

A half a century ago, at a time when as
yet virtually nothing was known about chemical reactions

in the nerve, the great biologist I.P. Pavlov wrote:

"Only   a study of the chemical-physical process
that occurs in the nerve structure will furnish us with the
real theory of   nervous phenomena. The phases of these
processes will give us an explanation of all the external
manifestations of nervous activity, of their sequence and
their ties." (Complete Works, vol.III, 1949, page 346).

In another place Pavlov said that the nature
of stimulation and inhibition of the nervous system and its
mechanism "again approaching the final answer, will be
exposed by chemistry and, finally, by physics". (Ibid,
page 503). And in one of his speeches he formulated the
concept "life" in the following manner: "Life is a complex
chemical process" (Complete Works, vol.V, 1949, page 86).
Thus, the statements of the viewpoints of two great natu-
ral scientists coincide literally word for word. These
general remarks on the subject of the meaning of separate
attributes of life, of their mutual subordination, were neces-
sary to define the place of metabolism phenomena in the
overall complex of phenomena characterizing living matter.

Passing to the basic problems of our thesis, we
must first stress that the very originality of living
objects, that differentiates them from inanimate objects,
naturally permits the expectation of original unrepeated

and unobservable peculiarities in the inanimate world, in chemical reactions that make up metabolism. It is these peculiarities that we will talk about.

The entire metabolism process as a whole, viewed in certain aggregates as well as in its numerous individual links that make up these aggregates, constitutes the most profound, convincing and unanswerable confirmation of the deepest penetration of the basic principle of dialectics, of, I would say, its first postulate (similar to the first postulate of thermodynamics), of that which Lenin characterized as the nucleus of dialectics – the concept of a phenomenon as the unity of opposites. This is ex-
pressed in the most complete manner in the/unity, in the
increasingly clear
umbreakable inner link and ultimate mutual penetrability and dependability of two great seemingly opposite channels of metabolism – assimilation and dissimilation. We are not now examining them   as opposing and independent phenomena. We are first of all amazed at their close inner ties and at their mutual interdependence.

At the recent broad discussion of the most promising lines of development of biochemical sciences in the next one or two decades, S. E. Severin very properly stressed three aspects of a biochemical approach to the fundamental problems of living matter. He expressed a sort of

triad: materialistic substrate, power and regulation of processes of metabolism. The balance of this article will be devoted precisely to this latter aspect, which up to the present time has not received the attention that it deserves.

The problem of the materialistic substrate, of course, has its own specifics - predominance of polymers, albumens and nucleinic acids. The power of living objects likewise is characterized by peculiar, specific traits. These include, first of all, the quantizing of this power, i.e. its accumulation and release in specific, discrete portions, followed by its transformation into a single, general, universal power fund in the form of energy-rich macroerg phosphate bonds. It follows that a specificity, of course, exists here. But it is necessary to stress mainly the third point, that places its specific

mark on the chemical nature of living things, these are the regulatory mechanisms, the manifestation of the regulation and autoregulation principle in separate metabolism processes and in their totality.

First, it would be useful, hoever, to say a few words about the means of exposing the fundamental aspects of metabolism processes, on the one hand, and to dwell again on the unity and multiplicity of laws and phenomena

of the living world in their chemical aspect, on the other.

The manner in which the special characteristics of metabolism are studied, basically, of course, cannot differ from the general manner of learning to understand nature and the laws of nature. This manner has been defined with final precision, in a laconical and monumental form by Lenin: "From a living observation to abstract thinking, and from there to actual practice - such is the dialectic road to the understanding of truth, of objective reality". It is the road of "joining analysis and synthesis - the examination of separate parts and of the totality, the joint summation of these parts." It is, finally, the road of "an infinite process of deepening of man's understanding of things, phenomena, processes, etc., the road from phenomena to actuality, and from a shallow actuality to a deeper, more generalized actuality." Fully in conformity with this general outline of the development of our know-ledge, the study of metabolism proceeds from observation to the creation of certain working hypotheses, to abstract thought, and, from it, to experiment, to actual practice.

One of the main features of this experiment in the area that interests us, one of the main problems that a scientist poses for himself, is the separation of phenomena studied by observation, the breaking up of comp-

lexities into their component parts.

This principle of study has placed its most typical mark on the entire course of the dvelopment of our knowledge with respect to the metabolism process. During the last decades the greatest successes have been attained along this course, and we have the right to say that the dynamic biochemistry of our times has developed under this aegis. Processes that formerly were accepted as the results of a simple, single-stage reaction, were found to be divisible step by step, into an ever growing number of component parts.

Fully analogous to what we see in the realm of study of the atomic nulcus, we may say that wo see before us a clear manifestation of the infinity of the number of natural phenomena, the appearance of ever newer problems that must be resolved as we overcome each of the barriers erected on our way.

It will be sufficient to cite some brief examples. Thus, the synthesis of urea, first formulated as a simple dehydration reaction of ammonium carbonate, now appears to be the result   of about ten strictly coordinated reactions.

The same is true of the oxidation of foodstuffs, where, in the place of a detonating gas reaction, i.e.

hydrogen oxidation, a lengthy chain of reactions was discovered, with dozens of links and a large number of distinct ferments.

This decomposition of complexities, of equilibrium reactions into components, is one of the typical features of the dvelopment of biochemical knowledge. It is the road from one reality to another deeper one.

It should be stressed that one of the very typical and specific features of metabolism is that which may be designated as a manifestation of unity in multiplicity, of similarity in diversity. This is manifested in the fact that over the entire breadth of the living world, from bacteria to the most highly complex tissue of the most highly developed organism, we encounter biochemical reactions not only similar in appearance, by their final effects, for example, but absolutely identical in all details of multistage mechanisms, in the sequence of the same reactions.

Especially surprising is not only the existence of the same substances, adenosin tri-phosphoric acid, for example, (ATF), that we encounter throughout the living world as a univeral link of cellular power, but especially the preservation throughout the ladder of evolution of strictly coordinated processes, that are at the base of the most important manifestations of metabolism.

In a microbe, as well as in a plant leaf and in the human
brain cell the process of anerobic disintegration of sugar
occurs in an absolutely identical fashion - by fermentation
or glucolysis. The same reaction sequence, the same order-
ly procedures and their connection are preserved along the
entire boundless course of evolution. The same is true of
the breathing of a cell. Here too identical mechanisms with
a varied and numerous collection of catalysts - flavinic,
pyridine and heminic ferments - function in the entire
diversity of living things.

It is perfectly evident that having once app
peared, these mechanisms are preserved throughout the
millions of years of the evolutionary process. This illus-
trates the remarkable perfection of a principle, once it has
been developed, its unusual durability. This is especially
surprising when we compare the stability of chemical catalysts
with the infinite variation of living organisms.
While there are external changes, the inner essence, in
many of its basic components is found to be virtually
identical. To think only, how many changes in form of the
totality of physiological functions have taken place in
organisms from the initial unicellular organism to man!
And throughout this infinitely long chain of the deepest
changes, the basic, fundamental processes of metabolism

have been preserved and carried by the living world. This
fact witnesses its unity.

We see here an unusual and profoundly signi-
ficant instance in principle, of the contrast between what
we might term the unlimited changeability and diversity
of living forms, on the one hand, and the amazing constance
and similarity and unchanging nature of that which might be
viewed as "content", i.e. the predominant portion of the
most important basic processes of metabolism, such as
breathing, fermentation, albumen synthesis, obviously right
up to phenomena of a higher order, above the molecular order
as, for example, the mechanics of registration of genetics
information and others, on the other.

In the midst of this unity of diversity,
we are struck by the coursing throughout the evolution, from
one limit of the evolutionary order to the other, not only
of a similar collection of catalysts , that perform impor-
tant functions in metabolism, but of the preservation along
this entire course of complex cyclical means of accomplish-
ment of certain basically important processes of metabolism.
It is precisely this principle of the cyclical course of a
series of most important conversions that constitutes
one of the most important features of the specifics of
metabolism reactions. Each separate link here does not

differ from the usual everyday chemical reaction. But
these separate reactions are found to be included in/ a chain of
extremely complex reactions. Here, the complete fusion of
two antagonistic and, seemingly mutually exclusive factors,
that are mutually penetrating, appears with remarkable
clarity -- the catalyst and the substrate.

Actually, the results of the actions of the
catalyst are to provoke a change in the substrate, that
is proceeding in a certain direction. One might say that
the catalyst leads to the disppearance of of the substra-
te. And what actually occurs in the case of the circular
cyclical processes of metabolism processes that we just
mentioned? The so-called Krebs cycle of tricarbon acids
may serve as a typical protoype of metabolism.

This cycle becomes reduced to the fact that
the substrate (an acetate molecule), that is the product
of foog disintegration, basically of fats or hydrocarbons,
becomes united with one of the components of the multistgge
catalytic cycle, and, in as part of this cycle, undergoes
changes. In the final analysis the acetate burns up, as a re-
sult of which two molecules -- carbonic acid and water --
-- appear. One might believe that the substrate temporarily
joins in the catalytic cycle and becomes subject to these
irreversible conversions into finished products. Actually,

however, that is nor se. Actually only one of the two carbonic acid molecules, comes from the acetate molecule (this may be verified by means of the isotope method), the other comes from the molecule of one of the intermediate links of the cycle, i.e. from the catalyst itself. As this catalytic cycle is completed, it is found that one of the carbons of the substrate entered into its composition, the substrate that became disintegrated in the preceding stage.

We may say that at this moment the cycle is the same as previously, but is no longer the same cycle. It is the same and not the same, because it changed, it absorbed material from the substrate. Thus, a substrate molecule becomes a structural, a chemical component of the catalytic mechanism itself. Therefore, to a certain extent, there occurs here a fusion of the concepts of substrate and catalyst. We could hardly expect even a distantly similar type of chemical or catalytic mechanisms to exist in the inanimate world. We have to see in this particular example, an important prototype of processes specifically natural only to living organisms. From the standpoint of the chemist, each separate link does not, of course, constitute characteristic peculiarity. There is nothing unusual in ney of these reactions, that differentiates it from well known organic chemistry reactions. But the whole in tote

acquires an entirely new, specifically characteristic aspect.

This may now be viewed as one of the characteristic and specific aspects of conversion of matter in living organisms, i.e. as one of the characteristic and specific aspects of metabolism.

Special attention should be directed toward another aspect that characterizes the course of chemical reactions of metabolism. This may be considered to be the existence of the phenomenon of autoregulation in the course of a whole series of biochemical conversions, including among them, most importantly, those that are the key, that play a leading part in the whole metabolism process complex.

Generallly accepted is the assertion that a living organism possesses mechanisms that adapt the metabolism activity to the existing conditions of the medium. In the case of more complex organisms, of course, such systems as the nervous system, the system of hormones play an enormous role. But regulation exists also in lower forms, where the higher regulating systems are lacking. This means that definite regulatory systems exist already in the most primitive stages. We have a right to assume that these primitive regulatory systems have been preserved

also in the higher forms of the organic world, in the same way as certain general and elementary catalytic systems have traversed the entire complex of the organic world.

How can cells adapt the rate of reactions to changing needs? Of course, this could be determined by the ratio of the amount of ferment to that of the substrate. On the other hand, this could also be determined by a change in the activity of the ferments.

First of all, it is important to establish what is actually the limiting factor, the factor that sets the rate of the reaction? Could the amount of ferment in tissues be such a factor that limits the reaction rate? One would think no. A report at the Physiological conference in Kiev in 1955 gave a computation of the amount of several ferments, for which data were availablr regarding amounts contained in living tissues. The molecular activity of these ferments is known. Knowing the amount of ferments and expressing this amount in moles, it is possible to compute the number of moles of substrate that must be subjected to conversion in a unit of time by the given amount of ferment. Such calculations were made for all ferments for which the necessary data were available. It was found that the power of the ferments greatly exceeds the actual rate of metabolic processes in the body. Therefore, the amount of fer-

ments is not a limiting factor. It is possible, however, that the activity of this or that ferment is retarded and that it does not work with full force. In this case it could become a limiting factor.

In order to judge the significance of this mechanism, we, unfortunately, do not possess sufficient experimental data at this time. In any event we can state that the activity of the ferment has been brought to a level where it does limit this process. We should give thought to the existence of another factor, of another participant of the enzyme reaction that limits its rate and that can thereby play the part of a regulator. Such a factor could be the amount of the substrate. Objections are possible to the effect that the amount of substrate in the cell usually is very great, and that the substrate can in no way determine the rate of a biochemical reaction. We are talking, however, not of initial substrates, not of matters such as glucose, for example, we are talking of substrates that play a part in the intermediate links of the process of metabolism. Cells contain, of course, a lot of glucose, fats, etc. The question is raised of the intermediate bonds that in essence compose inner metabolism. In such cases we have the right to state that it is precisely the content level of the substrate that often may be a limiting factor.

If that were not so, then an accumulation of intermediate matter would occur. In the mean time a characteristic aspect of metabolism is the fact that, as a rule, we do not observe this accumulation. These products disappear as rapidly as they are accumulated. They are always present in an almost indiscernible amount. It is natural that they could almost always be a limiting factor.

Krebs made such calculations, and they showed that, forexample, the average duration of the halflife of the separate components of a tricarboxylic cycle and, consequently, the average life duration of the products of final disintegration of carbons, entrained into this cycle, is expressed in magnitudes of the order of a few seconds. Under these conditions, therefore, an extremely small amount of substrate would be accumulated, that could be formed by the ferment in a few seconds. The addition of these intermediate products, therefore, speeds the process. It follows from this that in the given instance, as in a series of other cases, the rate of the metabolism reaction is limited by the concentration of this or that substrate. This in itself is already one of the specific aspects of metabolism, that we must take into account.

In other cases, we must take into account the existence of other regulatory mechanisms, observed in reac-

tions, where the rate is a function of other factors than the ferment and the substrate. Such reactions are factors that determine by themselves the rate of the process of metabolism. They are reactions that in scientific literature are designated by the term "pacemaker". In order to define such a concept, it is not so easy to find an equivalent term and express it in a single Russian word. They are reactions that set the rate of corresponding processes. They m may be termed tachostatic reactions, i.e. reactions that determine the rate of a metabolic process.

In physiology, it is often necessary to deal with such a concept of a rate regulator, a factor responsible for the rate. Thus, for example, taking the case of the activity of the heart, we speak of an agent that sets the rate of the cardiac rhythm. We encounter this concept especially in the realm of biochemical reactions. The are reactions that a "bottleneck" in the intensive course of the process of metabolism. It is perfectly clear that the total rate of a complex =rocess cannot be greater than that of the slowest bond. In the case of the chain being examined here, the slowest bond constitutes the tachostatic reaction.

A study of tachostatic reactions that are regulators of the intensity of the process of metabolism,

we encounter the existence of an extremely characteristic principle -- the principle of feedback.

The feedback principle has been adapted from cybernetics. It may exist in installations in which the controlled process in its course creates conditions unfavorable to its continuation, and thereby slows down the rate of the process.

There are many known feedback installations. An ordinary thermostat is one example. Among feedback systems are such processes, that may be termed regulating or tacho-static reactions.

The feedback principle is widely observed in biological phenomena. Take, for example, heat regulation: a higher temperature causes stimulation of heat regulating centers and a decreased heat production. Partial carbon dioxide pressure in alveolar air stimulates breathing centers, and brings about a heightened ventilation of lungs. All these are classical examples of feedback mechanisms at the level of a higher organism.

Of great importance is the fact that we deal with such feedback systems at the simplest, elementary and primary processes of metabolism. This must be viewed as one of the essential and characteristic features of metabolism. It casts its reflection on its entirety. There is

every reason to see in the functioning of feedback one of the principal manifestations of the specifics of metabolic processes in biological objects.

In its simplest, uncomplicated form, we observe the feedback principle even at the level of ordinary chemical reactions, in the form of the well known law of Le Chatelier. According to this law, in the case of /feedback chemical processes that have a perceptible heat effect, an increase in the temperature will speed up the endothermal reaction, i.e. the reaction that proceeds with an absorption of heat, and which, therefore, as it were, counteracts the rise in temperature. And, contrarywise, cooling, i.e. the taking away of heat, speeds up the exothermal reaction - the reaction that is accompanied by heat formation.

In biological processes of metabolism, the autoregulating phenomena are not accomplished by a simple displacement of equilibrium in individual feedback chemical reactions, but arise as a result of the totality of the chemical reactions, each of which does not separately have autoregulating properties, but, taken together, they form a system that discloses feedback properties. In principle, it is possible to imagine/ such a system, artificially created, from a combination of ordinary chemical reactions. There are no indications, however, of the existence of such

a system in the inanimate world, we therefore have the right
to see in them a qualitative peculiarity, a specific charac-
teristic of metabolism reactions, that take place in biolo-
gical objects.

The orderly procedures that we have pointed
out, already have attracted the attention of researchers,
but not nearly to the extent that would seem justified by
thier importance in principle, since in this case we are
having to do with a widescope phenomenon of general impor-
tance, one that lies at the base of the fundamental features
of the chemistry of k objects in the living world.

Here we cannot become involved in more specia-
lized details and, of necessity, will have to limit our-
selves to a very schematic description of some typical
concrete examples. The first example has to do with a com-
pound that occupies a central position in the entire
power generating, functional metabolism. This is adenosin
tri-phosphoric acid (ATF). It serves as the basic and
spontaneous source of energy for a great diversity of
biological functions, among which are muscular activity,
the realization of the most varied biological syntheses,
emission of light by certain organisms, the phenomena of
subdivision of cells and others. The decomposition of ATF
releases energy that serves as the motive power for all

these manifestations of living activity. Here, adenosin di-phosphoric acid (ADF) is formed, and a mineral phosphate. In turn, these materials - mineral phosphoric acid and ADF - resynthesize back to ATF as a result of breathing or glucolysis, the energy of which is accumulated in the phosphate bonds of the ATF. This may be schematically presented as follows:

Biological Function
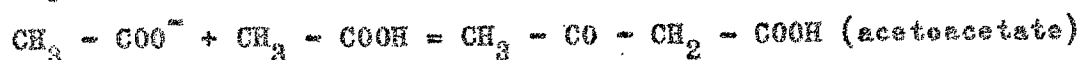
$$ATF \quad\quad ADF + H_3PO_4$$

breathing
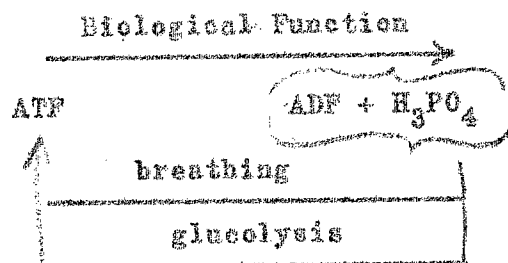
glucolysis

The more intensive the realization of this or that biological function, the more does ATF decompose, and the more ADF and mineral phosphate is formed. But the breathing and glucolysis processes, in their turn, require the presence of the mineral phosphate and of ADF, that serves as the a c c e p t o r of the phosphate. The great service performed by V. A. Belitser was his discovery that the presence of a phosphate acceptor may, under certain conditions, be the factor that determines the intensity of breathing, i.e. of the very same factor that leads to the d i s a p - p e a r a n c e of both the ADF and the phosphate by means of the so-called conjugate oxidized phosphorylation.

Thus, the appearance of p r o d u c t of biochemical
conversion (ADP), is a signal, is information for the
start of a process leading to the regenration of the initial
substance (ATP), as a result of the removal of the initially
formed products.

The autoregulation principle in this case
is manifested with great clarity. But in this system yet
another autoregulation process appears: the mutual interaction
of two basic energy sources of the cell - breathing and
fermentation (glucolysis). This interaction is expressed
in the damping of the energywise little-effective process
of glucolysis, by the more useful energywise process of
breathing. One of the mechanisms of this "Pasteur effect"
could be the competitive struggle for the phosphate acceptor,
which is ADF. There are reasons to believe that breathing
is capable of initially taking possession of this acceptor,
and at the point where the ADF content is so small that it
acts as a limiting factor, there is no longer enough of it
for the glucolytic system and glucolysis becomes damped.

Another example of autoregulation, of the auto-
matic direction of the process in one of the two possible
channels, is among reactions connected with the above-men-
tioned tricarbon cycle. Here too we witness certain elements
of the feedback mechanism. We are txixx talking about the

following: among the compounds that occupy key positions in processes of intermediate metabolism, is acetic acid. Its molecules are formed in the course of both carbohydrate and fatty metabolism. We are now interested in two forms of conversion of acetic acid, of acetate. Leaving aside the paticipation of coenzymes, we see that acetate may participate in two types of condensation reactions. Interacting with one of the bonds of the tricarbon cycle, with oxalacetic acid, the acetate condenses with it forming citrate (lemon acid). It is thus entrained into the chain of reactions of this cycle, and is finally oxidized, at which time a molecule of oxalacetic acid is again regenrated. This molecule, for the normal coursing of the cycle, must become condensed with the new acetate molecule. Such is the course of conversion of acetic acid in the breathing process of tissue. But when the processes of metabolism are disturbed, another type of reaction may take place: acetic acid becomes condensed not with oxalacetic acid but with another molecule of the same acetic acid, forming acetoacetic acid:

$$CH_3 - COO^- + COOH - CO - CH_2 - COOH -- citrate$$
$$CH_3 - COO^- + CH_3 - COOH = CH_3 - CO - CH_2 - COOH \; (acetoacetate)$$

Under conditions of normal intensity of oxidation processes, a sufficient amount of oxalacetic acid

is formed to enable all of the acetic acid, formed in the decomposition of fats and carbohydrates to combine with it and be entrained into the tricarbon cycle. This prevents the formation of acetoacetate, ensures the course of all links in the cycle chain and creates conditions favorable to the entrainment of new acetate molecules along the same course. But as soon as one of the links in the cycle is disturbed, even if it happens to be far removed from the point of actual entrainment of the acetic acid, and the signal of this fact, according to the feedback principle, in the form of the nonformation of oxalacetic acid, reaches the enzyme systems, that normally accomplish the condensation of the latter with acetate, and instead of the formation of citrate as a bond in the tricarbon cycle, the acetate molecules will now condense with each other, forming acetoacetic acid. Thus, the concentration of oxalacetic acid — one of the links in the catalytic tricarbon cycle — determines the fate of the acetic acid. If this concentration is sufficiently high, the condensation occurs with it, citrate is formed and the course of the cycle continues. If, however, the oxalacetic acid is absent, then a relatively stable acetoacetate is formed.

This example is significant also because it brings out yet another important specific aspect of bio-

chemical reactions. We see here that the fate of the molecule, that participates in the processes of metabolism, is decided at the crossroads of two possible further courses of of conversions. The fate of chemical compounds in a living object is decided at chemical crossroads. In the example that has been given, the fate of the acetic acid molecule was decided at the crossroads, represented in this case by two types of condensation reactions. The concentration of oxalacetic acid here serves as a regulating factor, that determines which of the two roads will be chosen.

Such a metabolism crossroads, at which the fate of the hexose molecule is decided - whether it will be subjected to oxidation or to fermentation - lies at the level of phosphoric hexose esthers: the compounding of the second leftover of phosphoric acid directs the molecule in the direction of anaerobic decomposition, while the removal of hydrogen predetermines the further/course of the decomposition.

oxidation

Such central points as the chemical crossroads for products of intermediate metabolism are of especial significance. We may view their existence also as one of the aspects of the specifics of the processes of metabolism. It would appear that it is precisely these points that in many cases have the nature of tachostatic reactions - reactions that

set the pace of biochemical processes discussed above.

And it is at the level of these points that the influences based on the principle of feedback most probably occur, influences that are such a powerful factor in the autoregulation of the chemistry of living things. There is every reason to believe that the great majority of external factors, in particular, poisons, medicinal preparations, exert their action precisely on the central points, at the crossroads, where the mechanisms of the type of feedback operate.

It is remarkable that the feedback principle, the principle of autoregulation and "selftuning", is manifested at the molecular-biological level in a virtually homogenous system, where no physical, or structural factors, no arrangements or mechanisms paticipate. It would not be an exaggeration to state that the discovery of the specific chemical aspects of metabolism examined above, is one of the most essential ahievements in the molecular biology of recent years.

the value of
It seems to me that/the feedback principle is not sufficiently recognized. At the same time it is deserving of especially serious attention in terms of its value in principle, and as an object of further experimental studies.   END
2166